Single-step antigen loading and TLR activation of dendritic cells by mRNA electroporation for vaccination in stage III and IV melanoma patients

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON32492

Source
ToetsingOnline

Brief title
Trimix DC vaccinations in melanoma patienten

Condition

- Skin neoplasms malignant and unspecified

Synonym
malignant melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: EU

Intervention

Keyword: DC vaccination, immune therapy, melanoma, Toll like receptors

Outcome measures

Primary outcome

The primary objectives of the study are to investigate the toxicity of TLR-DC

and Trimix DC by dose escalation of DC numbers.

Secondary outcome

In part II of the study, we will investigate immunological responses upon DC

vaccination.

Immunological responses are:

(a) The activation of immune cells in vivo.

(b) The immunological response induced with TLR-DC and Trimix DC loaded with

mRNA encoding melanoma-associated tumor antigens (gp100 and tyrosinase).

Safety and clinical efficacy are secondary objectives.

Study description

Background summary

Immunotherapy applying ex vivo generated and tumor-antigen-loaded dendritic cells (DC) has now successfully been introduced in the clinic. A limited, but consistent, number of objective immunological and clinical responses have been observed. Thusfar it remains unclear why some patients respond and others not, but there is a general consensus that the current protocols applied to generate DC may not result in the induction of optimal Th1 responses. We and others have demonstrated that DC maturation is one of the crucial factors, not only for effective DC migration but also to induce effective anti-tumor immune responses in cancer patients. Currently, the *golden standard* used to mature DC consists of a cocktail of pro-inflammatory cytokines (IL-1β, IL-6, TNFα) and

prostaglandin E2 (PGE2). Recent mouse data demonstrated, however, that maturation of DC by solely pro-inflammatory cytokines yielded DC that supported T cell clonal expansion, but failed to efficiently direct effector T cell differentiation. Interestingly, DC matured in the presence of Toll like receptor (TLR) ligands were able to induce full T cell effector function and unleashed more potent immune responses. We recently identified vaccines against infectious diseases that contain TLR ligands and are capable of inducing DC maturation. This knowledge provides a new application for these clinical applicable agents: clinical grade DC stimulators. A clinical grade DC maturation protocol is developed in which TLR ligands (preventive vaccines) and PGE2 are combined which resulted in the generation of mature DC that secrete high levels of the key cytokine IL-12. Moreover, these TLR-ligand matured DC (TLR-DC) induced T cells secreting at least 20-fold higher levels of the effector cytokines IFNγ and TNFα as compared to DC matured in the absence of TLR ligands.
In the group of Kris Thielemans and it was shown that the T-cell stimulatory capacity of peptide-pulsed DC can be greatly enhanced by providing them with three different molecular adjuvants through electroporation with mRNA encoding a so-called TriMix of CD40 ligand (CD40L), CD70, and a constitutively active form of TLR4 (caTLR4). The combination of CD40L and caTLR4 electroporation would mimic CD40 ligation and TLR4 signaling of the DC and generates phenotypically mature, cytokine/chemokine-secreting DC, as has been shown for CD40 and TLR4 ligation through addition of soluble CD40L and lipopolysaccharide. On the other hand, the introduction of CD70 into the DC would provide a costimulatory signal to CD27+ naive T cells by inhibiting activated T cell apoptosis and by supporting T cell proliferation.
In conclusion, these in vitro data demonstrate that both TLR-DC and Trimix DC are promising candidates to improve immunological and clinical responses in cancer immunotherapy.

Study objective

This is an exploratory study, consisting of two parts. In part I dose escalation is performed and the primary objective is the safety of different doses of TLR-DC and Trimix DC. In part II Trimix DC vaccination will be compared with TLR-DC vaccination and the primary objective of this part is the immunological response, with toxicity and clinical efficacy being secondary objectives. These studies will provide important data on the safety and immunological effects of TLR-DC and Trimix DC.

Study design

This study is an open label prospective exploratory intervention study.

Intervention

Stage III and IV melanoma patients will be vaccinated three times biweekly with mature DC injected directly into the lymph node loaded with mRNA encoding tumor-associated antigens gp100 and tyrosinase and pulsed with KLH as an immune control antigen. In part I we will perform a dose-finding study in 5 stage IV patients with DC electroporated with CD40L, CD70 and caTLR4 (Trimix DC) and 5 stage IV patients with DC matured in the presence of the vaccines BCG, Typhim and Act-HIB (TLR-DC). If no toxicity is observed, we will continue with part II of the study. In part II we aim to include 24 evaluable patients. In this part we aim to include in both arm A (Trimix DC) and arm B (TLR-DC), 7 stage IV patients and 5 stage III patients within 2 months after radical regional lymphnode dissection.

Study burden and risks

Based on the experience with our cytokine/PGE2-matured DC and TLR-DC, and the studies performed by Dr. Kris Thielemans and Dr. Bart Neyns (VU Brussels, Belgium) exploiting Trimix DC (thusfar 29 patients treated without toxicity: 4 times 12.5 million Trimix DC injected intradermally per vaccination timepoint), we expect that the DC will be well tolerated. Common and expected side effects of DC vaccination are usually mild and include flu-like symptoms and local reaction at injection site, both CTC grade 1.
Patient material that will be requested during the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

All patients:
- histologically documented evidence of melanoma
- stage III or IV melanoma according to the 2001 AJCC criteria
- melanoma expressing gp100 (compulsory) and tyrosinase (non-compulsory)
- WHO performance status 0-1 (Karnofsky 100-70)
- life expectancy >3 months
- age 18-70 years
- no clinical signs or symptoms of CNS metastases
- WBC >3.0×109/l, lymphocytes >0.8×109/l, platelets >100×109/l,
serum creatinine <150 µmol/l, serum bilirubin <25 µmol/l
- normal serum LDH (<=450 U/l)
- expected adequacy of follow-up
- no pregnant or lactating women
- written informed consent
and in addition:
Stage III melanoma
- interval since radical regional lymphnode dissection is <2 months
Stage IV melanoma
- at least one unidimensional measurable target lesions according to RECIST, not previously irradiated, and no significant symptoms of disease requiring other palliative treatments

Exclusion criteria

- prior chemotherapy, immunotherapy or radiotherapy <4 weeks prior to planned vaccination or presence of treatment-related toxicity
- history of any second malignancy in the previous 5 years, with the exception of adequately treated basal cell carcinoma or carcinoma in situ of the cervix
- serious active infections, HbsAg or HIV positive or autoimmune diseases or organ allografts
- concomitant use of immunosuppressive drugs
- known allergy to shell fish (since it contains KLH)

- rapidly progressive disease
- any serious clinical condition that may interfere with the safe administration of DC

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-05-2010
Enrollment:	34
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	02-02-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-02-2010

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-05-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-06-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-015737-73-NL
CCMO	NL29825.000.09

Study results

Date completed:	01-05-2012
Actual enrolment:	28